Palladium-Catalyzed α-Stereoselective *O*-Glycosylation of O(3)-Acylated Glycals

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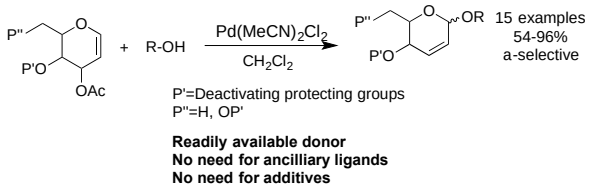
Supporting Information Placeholder

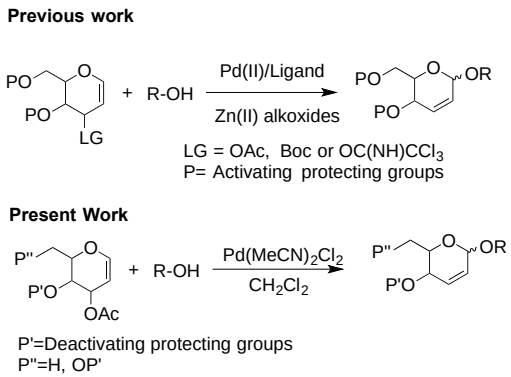


ABSTRACT: $Pd(MeCN)_2Cl_2$ enables the alpha-stereoselective catalytic synthesis of 2,3-unsaturated *O*-glycosides from O(3)-acylated glycals without the requirement for additives to pre-activate either donor or nucleophile. Mechanistic studies suggest that, unlike traditional (η3-allyl)palladium-mediated processes, the reaction proceeds via an alkoxy-palladium intermediate that increases the proton acidity and oxygen nucleophilicity of the alcohol. The method is exemplified with the synthesis of a range of glycosides and glycoconjugates of synthetic utility.

Interest in the synthesis of oligosaccharides and glycoconjugates continues, because of their involvement in many biological processes, some of which are disease-related[1] and because there is a need to efficiently access glycan-based tools to study these processes.[2,3] The chemical synthesis of complex carbohydrates generally involves the coupling of a fully protected glycosyl donor with a suitably protected glycosyl acceptor (R-OH).[4-7] In many instances, these reactions lead to a mixture of two stereoisomers. Thus, having the ability to direct the stereoselective formation of glycosidic linkages with specific reagents in a catalytic manner is highly desirable.

The Ferrier glycosylation reaction involves the allylic coupling of a nucleophile to a glycal bearing a leaving group at C3, which leads to the corresponding 2,3-unsaturated glycoside.[8-12] The products of this transformation are versatile chiral intermediates in the synthesis of a variety of important compounds from nucleosides, and antibiotics to several biologically-active natural products.[13-17] Traditionally, a stoichiometric Lewis acid is required to facilitate the allylic rearrangement,[17] which has limited the utility of this very attractive transformation. More recently, transition metal catalysis has been successfully applied to oligosaccharide synthesis as an improved alternative to traditional glycosylation promoters, including examples involving glycal starting materials where the allylic feature is typically exploited for activation using a metal catalyst.[18-30] In this context, palladium (II)-catalysis has been used for the direct activation of 1,2-unsaturated glycals to yield the corresponding 2,3-unsaturated products with good-to-excellent selectivities and yields, and the reaction is thought to proceed via π-allyl intermediates.[19,26] However, despite employing activated glycals as the starting materials to facilitate the reaction, the poor reactivity of both the glycal donors and alcohol acceptors for a η3-metal-mediated reaction has been a major challenge to this approach.[31-33] Elegant efforts from Lee et al.[34] to overcome this issue, employ zinc(II) alkoxides, in addition to $Pd(OAc)_2$ and ancillary ligands, to activate both the acceptor for the nucleophilic addition, and the leaving group for the ionization. More recently, the Nguyen group reported a palladium-catalyzed Ferrier-type glycosylation using glycal donors with a trichloroacetimidate leaving group at C-3. Similarly, prior activation of the glycoside acceptor is required via a zinc alkoxide for the reaction to proceed.[35]

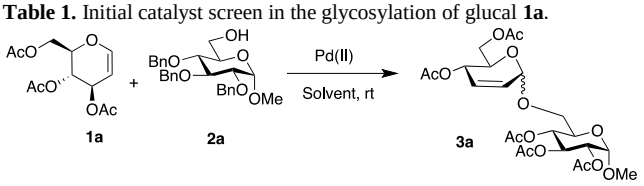
Scheme 1. Palladium-catalyzed synthesis of 2,3-unsaturated glycosides.



Prompted by our interest in the development of catalytic methods for the synthesis of *O*-glycosides from glycal starting materials,[36-39] we undertook synthetic studies towards the palladium catalyzed stereoselective synthesis of 2,3-unsaturated *O*-glycosides (Scheme 1). Herein we report an additive free Pd(II) stereoselective synthesis of *O*-

glycosides from "disarmed" glycals that employs only $Pd(MeCN)_2Cl_2$; a reaction that we propose proceeds via an alkoxypalladation-type mechanism to yield the glycoside products with high α-stereocontrol.

Table 1. Initial catalyst screen in the glycosylation of glucal **1a**.

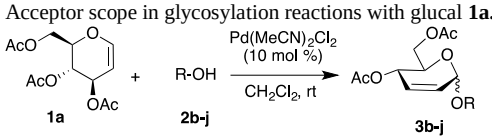


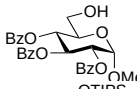
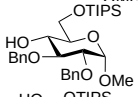
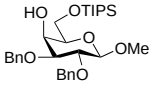
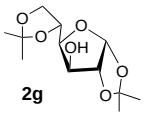
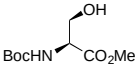
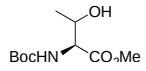
Entry	Catalyst (Loading mol%)	Solvent	Time (h)	Yield[a] (%)	α:β[a]
1	$Pd(MeCN)_2Cl_2$ (2.5)	CH_2Cl_2	24	40	5:1
2	$Pd(MeCN)_2Cl_2$ (5)	CH_2Cl_2	24	52	5:1
3	$Pd(MeCN)_2Cl_2$ (10)	CH_2Cl_2	5	88[c]	6:1
4	$Pd(CH_3CN)_2(OTs)_2$ (10)	CH_2Cl_2	17	88	3:1
5	$Pd(CH_3CN)_4(OTf)_2$ (10)	CH_2Cl_2	5	N/A	N/A[b]
6	$Pd(CH_3CN)_4(BF_4)_2$ (10)	CH_2Cl_2	5	90	2.3:1
7	$Pd(OAc)_2$ (10)	CH_2Cl_2	5	N/A	-
8	$Pd(MeCN)_2Cl_2$ (10)	PhMe	24	18	-
9	$Pd(MeCN)_2Cl_2$ (10)	CH_3CN	15	traces	-
10	$Pd(MeCN)_2Cl_2$ (10)	CH_2Cl_2	5	N/A[d]	N/A
11	$Pd(MeCN)_2Cl_2$ (10)	CH_2Cl_2	5	N/A[e]	N/A
12	$Pd(MeCN)_2Cl_2$ (10)	CH_2Cl_2	5	N/A[f]	N/A

[a] Determined by crude ^{1}H-NMR; [b] inseparable mixture of products; [c] isolated yield; [d] addition of N-phenyl-2-(di-tert-butylphosphino)pyrrole (0.2 equiv.); [e] addition of tricyclohexyl-phosphine (0.2 equiv.); [f] addition of $Cu(OTf)_2$ (0.1 equiv). N/A = not applicable

The ligand and counter ion in a transition metal catalyzed reaction plays a key role in stabilizing and activating the central metal atom and fine-tuning the selectivity of the transformation.[40] Thus, our initial studies began by screening a series of commercial palladium (II) catalysts for their ability to promote the Ferrier-type stereoselective glycosylation of peracetylated glucal **1a** with glucoside acceptor **2a**[12] in the presence of different catalyst loadings and solvents at room temperature. As summarized in Table 1, 10 mol% proved to be the optimum catalyst loading for reactions that used $Pd(MeCN)_2Cl_2$ in CH_2Cl_2 (88% of **3a**, entry 3), with reactions being much slower when lower catalyst loadings were used (entries 1 and 2). To further investigate the effect of the catalyst, a series of different Pd (II) catalysts (10 mol %) in CH_2Cl_2 were also screened in the glycosylation reaction (Table 1, entries 4-7). It was found that removing or replacing the Cl counter-ion by a *p*-toluenesulfonate was detrimental to reaction rate and stereocontrol, while use of tetrafluoroborate eroded the α-selectivity. The use of trifluoromethanesulfonate led to an inseparable complex mixture of products. Moreover, no reaction occurred when $Pd(OAc)_2$ was employed, demonstrating that $Pd(MeCN)_2Cl_2$ was the optimal catalyst. Next, we decided to explore solvent effects and the addition of ancilliary additives. The use of acetonitrile or toluene as the solvent at room temperature was detrimental to yield (entries 8 and 9), as was the addition of phosphine ligands (N-phenyl-2-(di-*tert*-butylphosphino)-pyrrole or tricyclohexylphosphine) or $Cu(OTf)_2$ to the reaction (entries 10 - 12).

Table 2. Acceptor scope in glycosylation reactions with glucal **1a.**

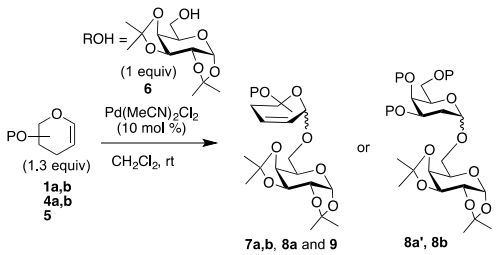


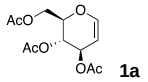
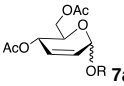
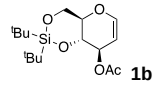
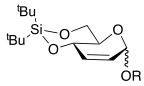
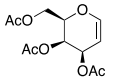
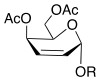
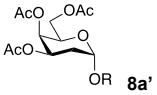
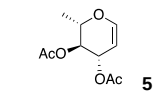
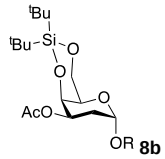
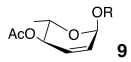
Entry	ROH		Time (h)	Yield (%)[a]	α:β[b]
1		**2b**	3	97	□□□
2	BnOH	**2c**	3	97	9:1
3		**2d**	7	90	9:1
4		**2e**	16	68	9:1
5		**2f**	17	65	20□1
6		**2g**	17	70	4:1
7		**2h**	17[c]	68	3:1
8		**2i**	17[c]	64	>99:1
9		**2j**	15[c]	90	>99:1

[a]Yield of isolated product; [b] Determined by crude ^{1}H-NMR. [c] Reaction carried out at 50 °C

Having established the optimum reaction conditions, our attention turned to exploring the substrate scope of the coupling reaction between **1a** and a range of other OH nucleophiles **2b**-**j** (Table 2). In all cases, the reactions proceeded smoothly within 3-17 h and in good to excellent yield and a clear preference for the α-products. These successes demonstrate that the catalytic system tolerates the presence of common alcohol and amine protecting groups such as acetals, ethers, esters and carbamates. Glycosylations with primary alcohols **2b**-**d** afforded the corresponding 2,3-unsaturated glycosides in 90-97% yield within 3-7 h and with a 9:1 α□β□ratio (entries 1-3). Reactions with secondary alcohols such as glycosides **2e**-**g** (Table 2, entries 4-6) prove to be more challenging and required longer reactions times (15-17 h). Moreover, in the case of Boc-protected serine **2h**, threonine **2i** or N-hydroxysuccinimide **2j**, besides longer reaction times, 50 °C reaction temperatures were required (entries 7-9). Under these conditions, the desired products were isolated with similar high α□selectivity (>99:1 to 3:1, α□β ratio) and yields of 64-90%, with the lower yields being attributable to the more hindered nature of the secondary OH nucleophiles.

Table 3. Reaction of glycals **1b**, **4a**, **4b** and **5** with model glycoside acceptor **6**.



Entry	Donor	Product	Time (h)	Yield (%)[a]	α:β[b]
1	 **1a**	 **7a**	6	85	9:1
2	 **1b**	 **7b**	18	54	9:1
3	 **4a**	 **8a**	15	65	>99:1
		 **8a'**		20)	
4	 **4b**	 **8b**	18	90	>99:1
5	**5**	 **9**	7	76	>99:1

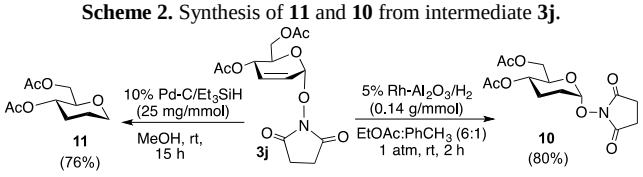
[a] Isolated yield. [b] Determined by ^{1}H-NMR.

Our attention next turned to exploring the scope of the glycal donor. It has been shown that glycal conformation can modulate both reactivity and stereoselectivity of these reactions.[17] It has been proposed that the conformational equilibria of glycals ($^4H_5$ *vs* $^5H_4$) is influenced by several contributing factors such as the vinylogous anomeric effect (VAE),[41] which dictates a preferred pseudoaxial orientation of the acyloxy group at C-3, and thus favours a $^5H_4$ conformation; also important are 1,3-diaxial interactions, which compete with the VAE and are influenced by the substituents at C-5, and the orientation of the C-4 substituent. In the case of galactal, where C-4 is axial, as opposed to equatorial as in glucals, the equilibrium is shifted towards the $^4H_5$ form. Glycal substrates that favour a bigger shift towards $^5H_4$ conformations (e.g. glucals) undergo rearrangement/substitution more readily than their corresponding counterparts (e.g. galactals).[42,43] Furthermore, the use of conformationally-constraining protecting groups can also affect both the reactivity and stereocontrol of reactions involving glycal donors[38,44,45]

To that end, a series of differentially protected deactivated glycals were prepared. They included peracetylated glucal **1a**, galactal **4a** and L-rhamnal **5**, conformationally-constrained **1b** and **4b**, and all were reacted with **6** as the model acceptor (Table 3). In general, moderate-to-good yields and α-selectivities were obtained in most examples leading to the formation of 2-deoxy and 2,6-dideoxy Ferrier-type products (entries 1, 2, 3 and 5), with peracetylated glucal **1a** affording the best yields (85%) for the formation of **7a** as a 9:1 α:β □□□□□□□□, while the 4,6-*O*-constrained glucal **7b** afforded the product in a lower yield of 54%, with stereoselectivity unchanged. As predicted, the reaction with galactal **4a** was less selective towards Ferrier-rearrangement and gave a mixture of 2,3-unsaturated product **8a** (65%) and 2-deoxyglycoside **8a'** (20%) with almost complete α-stereocontrol (>99:1). Unexpectedly 4,6-O-siloxane protected galactal **4b** yielded only the 2-deoxyglycoside **8b** in 90% yield with high α-selectivity, which we attribute to the additional constraint imposed by the siloxane protecting group, which reduces the reactivity of the glycal towards allylic rearrangement in favour of direct glycosylation.

To demonstrate the synthetic utility of 2,3-unsaturated glycosides, reduction of *O*-linked-*N*-hydroxysuccinimide **3h** was carried out with 5% Rh-Al_2O_3/H_2 to yield the corresponding 2,3-deoxyglycoside **10** in 80% yield, while treatment of **3h** with Et_3SiH and catalytic amounts of 10% Pd/C afforded hydropyran **11** in 76% yield (Scheme 2), which gives access to a chiral scaffold that can be further developed as a medicinally-active compound.[46,47]

Scheme 2. Synthesis of **11** and **10** from intermediate **3j**.

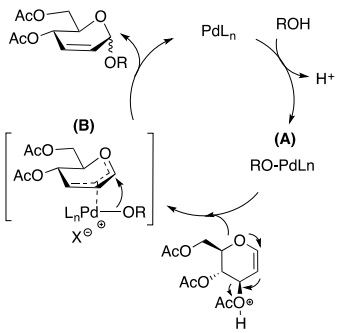


To probe the mechanism of the palladium-catalysed Ferrier reaction, ^{1}H-NMR spectroscopy studies of glucal **1a** and $Pd(MeCN)_2Cl_2$ in CD_2Cl_2 did not show any changes in the spectra (Figure S1, ESI), suggesting that the palladium catalyst does not interact with the alkene functionality in "disarmed" glycal donors. Indeed, previous results from our group have shown that mixtures of $Pd(MeCN)_2Cl_2$ and perbenzylated galactal (an "armed" or activated donor) clearly showed downfield H-shifts associated with alkene protons in the glycal (from δ□6.37 ppm to 6.20 and 6.03 ppm).[40] NMR studies of acceptor **2a** and $Pd(MeCN)_2Cl_2$ showed upfield shifts corresponding to the OH signal in **2a** (from 1.86 ppm to 1.75 ppm) (Figure S2, ESI), while ^{1}H-NMR spectra of a mixture containing **1a**, **2a** and $Pd(MeCN)_2Cl_2$ in CD_2Cl_2, collected after 10 min and 1 h, showed the disappearance of the OH proton from **1a** and the appearance of new signals corresponding to the Ferrier product (See ESI, Figure S4 for details). These results suggest that the reaction proceeds via alkoxypalladation of the OH nucleophile.

As proposed in Scheme 3, palladium-catalyzed allylic rearrangement of deactivated glycals with alcohol nucleophiles involves an initial insertion of Pd into the RO-H bond, rather than the traditional pathway of palladium-mediated alkene activation,[19,26] to produce alkoxypalladium species (A) with concomitant H^+ release from the OH nucleophile.[48] Proton catalyzed allylic rearrangement can now take place, which leads to the formation of a transient oxocarbenium ion that can undergo reversible coordination with complex (A) from the α-face preferentially, likely due

to sterics and a favorable anomeric effect,[49,50] and formation of a short-lived intermediate (B). Concomitant deoxypalladation and nucleophilic addition of the activated oxygen in a stereoselective manner then yields the 2,3-unsaturated glycosides.[51]

Scheme 3. Proposed mechanism.



In summary, we have described a practical and stereoselective method for the preparation of 2,3-unsaturated glycosides using commercial $Pd(MeCN)_2Cl_2$ in CH_2Cl_2 from O(3)-acylated glycals. This mechanistically interesting and unprecedented reaction is mild and proceeds with good-to-excellent yields and high selectivity for the α-anomer. The method utilizes commercial starting materials and is widely applicable to a range of nucleophile acceptors. We exemplify the utility of this approach in the stereoselective synthesis of a series of disaccharides, glycosylamino acids and other glycoconjugates including saturated chiral scaffolds of medicinal relevance.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data; this material is available free of charge *via* the Internet at http://pubs.acs.org.

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